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Research Paper

Synthesis, Characterization, and Antibacterial Activity of Some Mesalazine Derivatives

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Abstract
Mesalazine, often referred to as mesalamine or 5-aminosalicylic acid (5-ASA), and its derivatives are some of the first medications to be approved for treating digestive tract inflammations, including ulcerative colitis and mild to moderate Crohn's disease. Sulfasalazine, discovered in 1938 for therapeutic use, was the first mesalazine derivative. High yields of four different mesalazine derivatives were synthesized, including two Schiff bases and two azo compounds. The present study involved the synthesis of Schiff bases through the reaction of mesalazine with pyrrole-2-carbaldehyde or indole-2-carbaldehyde, resulting in the formation of 5-(((1H-pyrrol-2-yl)methylene)amino)-2-hydroxybenzoic acid (1) or 5-(((1H-indol-2-yl)methylene)amino)-2-hydroxybenzoic acid (2), respectively. The synthesis of azo compounds involved the coupling of mesalazine with sulfamethoxazole or pyridoxine, resulting in the formation of 5-amino-2-hydroxy-3-((4-(N-(5-methylisoxazol-3-yl)sulfamoyl)phenyl)diazenyl)benzoic acid (3) or 2-hydroxy-5-((5-hydroxy-3,4-bis(hydroxymethyl)-6-methylpyridin-2-yl)diazenyl)benzoic acid (4), respectively. The identification of the synthesized compounds was carried out using IR and 1H-NMR spectroscopy. Antibacterial assessment of the synthetic compounds was performed in vitro against gram-negative bacteria (such as *Escherichia coli* and *Pseudomonas aeruginosa*) and gram-positive bacteria (*Staphylococcus aureus*). The antibacterial activity studies demonstrated that against *Escherichia coli* and *Staphylococcus aureus*, the Schiff base compounds are more active than azo compounds. Compound 1 showed the highest activity, resulting in a 23 mm inhibition zone against *E. coli* at 1000 μg/mL. In contrast, the antibacterial activity of compound 2 was observed to be 25 mm against *S. aureus* at the same highest concentration.

Keywords
Mesalazine, Schiff Bases, Azo Compounds, Antibacterial Activity, Modification of Drug

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1. INTRODUCTION

Modifying the chemical molecules of commercially available medications is one of the most critical aspects of pharmacological development. Molecular modification involves changing the chemical structure of drugs away from their active site, which can impact their efficacy and ability to treat certain diseases. Thus, a new derivative of the drug molecule is prepared using different chemical reactions with physicochemical properties other than the original drug (Ye and van Langenberg, 2015). The substance mesalazine, used to treat inflammatory bowel diseases like Crohn's disease and ulcerative colitis, is one essential medicine whose chemical structure has undergone modifications (Yasutomi et al., 2019). Mesalazine has additional biological activities; it has been utilized as an antioxidant against oxygen and nitrogen free radicals (Yousefi et al., 2017), anti-ulcer (Beiranvand, 2021), against colorectal cancer (Dixon et al., 2021), and antimicrobial activity (Zhang et al., 2018; Cevallos et al., 2021).

Several pharmaceutical dosage forms of mesalazine derivatives are utilized in the drug market to treat UC, focusing on aminosalicylic acids and their associated derivatives. The most important derivatives are salazosulfapyridine (SASP), olsalazine, and mesalazine (Zhang et al., 2015).

The chemical structure of mesalazine is of great importance in the process of chemical modification on this molecule, as it contains in its structure two groups, carboxyl and amine groups, and these two groups are easily subject to many types of chemical reactions, allowing the formation of many types of derivatives (Yuri et al., 2020). Within the design of prodrugs as derivatives of the drug mesalazine, many polysaccharides were used by linking them using ester bonds of the carboxyl group because they are considered non-toxic. Through the polysaccharide compounds, it is possible to observe the mutation in the characteristics of these compounds through their

absorption from the small intestine; it is also soluble in water (Sardo et al., 2019). The other type of modification is on the amino group, and the prodrugs of mesalazine can be prepared by linking them with amino acids. Based on these functional groups, amino acids can be connected via an ester (Yousefi et al., 2015) or amide bond, and an azo group (Abdel Alim et al., 2005) can be synthesized. In particular, when an amide bond is used, the synthesized compound is similar in structure to a dipeptide (Monbaliu, 2016; Taheri-Ledari et al., 2022; Tosi et al., 2022).

In this study, four synthesized mesalazine derivatives were tested for their potential antibacterial activity against two types of Gram-positive and Gram-negative bacteria. Two are derivatives of Schiff bases (1 and 2), and the other are derivatives of azo dyes (3 and 4).

2. EXPERIMENTAL SECTION

2.1 Materials

The reagents and solvents utilized in this study were of reagent-grade quality and were procured from Merck and Sigma-Aldrich. Solid materials were used without additional purification, while liquid materials were subjected to double distillation. The Gallenkamp Thermal Point Apparatus was utilized to determine the uncorrected melting points. The FTIR 8400S SHIMADZU (Japan) was utilized to record infrared spectra in KBr pellets at Basrah University's College of Science. DMSO-d6's 1H-NMR spectra were measured at 500 MHz using a Bruker AC 200 FT-NMR spectrometer with TMS as an internal reference, (Greece). The CHN elemental analyzer flashes EA 1112 series was utilized to conduct the Elemental Microanalysis (CHN) on the synthesized compounds, (Thermo Finnigan).

2.2 Methods

2.2.1 Synthesis of Compounds

Schiff bases Synthesis 5-(((1H-pyrrol-2-yl)methylene)amino)-2-hydroxybenzoic acid (1) and 5-(((1H-indol-2-yl)methylene) amino)-2-hydroxybenzoic acid (2):

In the mixture that contained 0.01 mole (1.51 g) of 5-amino salicylic acid that had been dissolved in 15mL of ethanol, 0.01 mole of either pyrrole-2-carboxaldehyde or indol-2-carbo xaldehyde that had also been dissolved in 15 mL of ethanol was added, and then 1 mL of glacial acetic acid was added to the mixture. The mixture was stirred continuously for sixty minutes at room temperature. To get rid of any unreacted substances, the yellow precipitate that formed, as a result, was filtered out and then washed with cold methanol. Ethanol was used to recrystallize the products that were the result (Vhanale et al., 2019; Warad et al., 2020).

(1): A pale yellow crystal was obtained with a yield of 90%. The melting point was within the range of 187-189 °C. The infrared spectrum of the compound, obtained using KBr, showed absorption bands at 3305 cm^{-1} (O-H), 3010 cm^{-1} (C-H, aromatic), 1687 cm^{-1} (C=N, azomethine), 1606 cm^{-1}, and 1508 cm^{-1} (C=C), as well as at 1253 cm^{-1} and 1145 cm^{-1} (C-N, C-O). The 1H NMR spectrum of the compound in DMSO-d6 solution displays signals at δ = 12.80 (broad, 1H, carboxylic acid), 10.39 (singlet, 1H, hydroxyl), 9.25 (singlet, 1H, amine), 8.61 (singlet, 1H, imine), and a range of signals between 6.53 and 8.13. (m, 6H, Ar-H). Anal. Calc. (Found) for $C_{12}H_{10}N_2O_3$ (230.22): C, 62.61 (61.95); H, 4.38 (4.54); N, 12.17 (12.32).
(2): Crystal in a dark yellow color, with a yield of 92%, melting point in the range of 174-176 degrees Celsius, and the following IR (KBr) spectrum: v (cm^{-1}) = 3386 (O-H), 3010 (C-H, aromatic), 1656 (C=N, azomethine), 1600, 1510 (C=C), 1238, 1165 (C-N, C-O). 1H nuclear magnetic resonance (DMSO-d6): = 6.92-7.90 (m, 8H, Ar-H), 8.84 (s, 1H, CH=N), 8.99 (br, 1H, NH), 10.25 (s, 1H, OH), 12.69 (br, 1H, COOH). Anal. Calc. (Found) for $C_{16}H_{12}N_2O_3$ (280.28): C, 68.56 (67.87); H, 4.32 (4.22); N, 9.99 (10.21).

The present study involves the synthesis of two compounds, namely 5-amino-2-hydroxy-3-((4-(N-(5-methylisoxazol-3-yl)sulfamoyl)phenyl)diazenyl) benzoic acid (3) and 2-hydroxy-5-((5-hydroxy-3,4-bis(hydroxymethyl)-6-methylpyridin-2-yl) diazenyl)benzoic acid(4).

Diazotization was accomplished by dissolving 0.025 mol of 5-aminosalicylic acid or sulfamethoxazole in 5 mL of 2 M hydrochloric acid. After that, the solution was placed in an ice bath until it reached a temperature of 0-5 degrees Celsius, then kept at that temperature. A solution of sodium nitrite (5 mol, 2 g) in water (5 mL) was added drop by drop while the mixture was continuously stirred for ten minutes at the same temperature.

General procedure for preparation of azo dyes: The coupling reaction was performed by gradually adding the diazonium solution of 5-aminosalicylic acid or sulfamethoxazole to the coupling component solution, which had been prepared by combining a suspension of one mmol of pyridoxine (0.2056 g) or one mmol of 5-aminosalicylic acid (0.253 g) (Scheme 1) in 10 mL of water with sodium hydroxide (0.002 mmol) dissolved in 15 mL of water. During this procedure, the pH was between 9 and 10, while the temperature was maintained at 0 to 5 degrees Celsius. The mixture was agitated for 6 hours, and the pH was lowered to about six. Overnight, the mixture was kept. Filtration was used to collect the precipitated crude dyes, which were then washed with solvents such as water, ethanol, and acetone (Benkhaya et al., 2020; Kareem Samad, 2017).
(3): Powdered orange, 80% yield; melting point below 306 degrees Celsius; infrared (KBr) spectral lines: v (cm^{-1}) = 3412 (O-H), 1591 (C=N), 1511 (C=C), 1463 (N=N), 1300 (C-H, Aliph), 1174, 1091 (C-N, C-O). For the hydrogen atom(1H) in DMSO-d6, the NMR spectrum looks like this: = 12.56 (br, 1H, COOH), 10.40 (s, 1H, OH), 11.20 (br, 1H, NH), 6.86-8.02 (m, 7H, Ar-H), 5.36 (s, 2H, NH_2), 1.91 (s, 3H, CH_3). Anal. Calc. (Found) for $C_{17}H_{15}N_5O_6S$ (417.40): C, 48.92 (48.67); H, 3.62 (3.52); N, 16.78 (16.61).
(4): The color is dark purple, the yield is 85%, the melting point is below 350 degrees Celsius, and the infrared spectrum looks like this: IR (KBr): v (cm^{-1}) = 3425 (O-H), 1645 (C=N), 1500 (C=C), 1587 (N=N), 1384 (C-H, Aliph), 1272 (C-N, C-O). ^{1}H NMR (DMSO-d6): δ = 12.77 (br, 1H, COOH), 10.35

(s, ^{1}H, OH), 9.79 (s, 1H, OH pyridoxine), 7.25-7.86 (m, 3H, Ar-H), 5.63 (s, 2H, OH aliphatic), 4.21 (s, 4H, CH_2), 2.37 (s, 3H, CH_3). Anal. Calc. (Found) for $C_{15}H_{15}N_3O_6$ (333.30): C, 54.05 (54.32); H, 4.54 (4.42); N, 12.61 (12.71).

2.2.2 Antibacterial Evaluation

Pathogenic strains of Gram-positive (*Staphylococcus aureus*) and Gram-negative (*Escherichia coli* and *Pseudomonas aeruginosa*) were used to investigate the antibacterial activity of the prepared compounds using the Filter Paper Disc Diffusion Method (Kifby-Bauer Method). This method measured the inhibition zone in mm around these bacteria. A dimethyl sulfoxide solvent was used to prepare a stock solution of 1000 μg/mL for each compound, which was subsequently stored at 4-8 °C until utilized. The Mueller Hinton agar plates were inoculated using a sterile cotton swab dipped into the inoculum. The swab was then evenly streaked in three directions across the entirety of the Petri-dish surface. Discs of filter paper measuring 6 mm in diameter were saturated with a solution of tested compounds at a concentration of 1000 mg/mL and various other diluted concentrations. The impregnated discs were subsequently dried and positioned onto an agar plate inoculated with Gram-positive and Gram-negative bacteria cultures (Salman, 2019; Mohammed-Ali and Jasim, 2019).

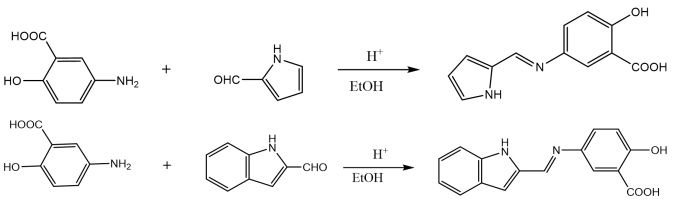

Figure 1. Compounds One and Two Synthesis

3. RESULTS AND DISCUSSION

3.1 Chemistry

The synthesis of two products (1 and 2) was achieved by condensing the 5-aminosalicylic acid compound with pyrrole-2-carboxaldehyde or indol-2-carboxaldehyde in refluxed ethanol solvent, with the addition of a tiny amount of glacial acetic acid. The resulting yellow crystals were analyzed using IR spectroscopy, revealing significant absorption broad bands at v 3305 and 3386 cm^{-1} for compounds (1) and (2), respectively. These bands were due to the vibrations caused by stretching of O-H for phenolic and carboxylic groups, as depicted in Figure 1. The appearance of a distinct band at 1658 and 1656 cm^{-1} (Bartyzel, 2017) (for compounds 1 and 2, respectively) is indicative of the C=N vibrations that stretch the azomethine fragment, thereby providing compelling evidence for the formation of Schiff bases.

Four singlet signals were found in the ^{1}H-NMR spectrum of compound (1). Two of these signals referred to hydroxyl groups of carboxylic and phenol of salicylic fragment at δ 12.80

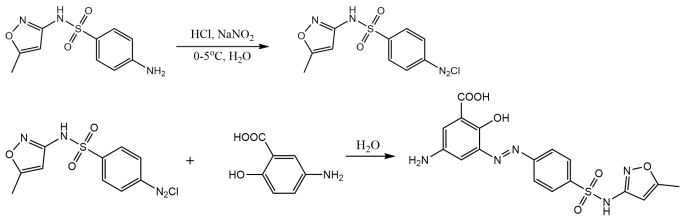

Figure 2. Compound Three Synthesis

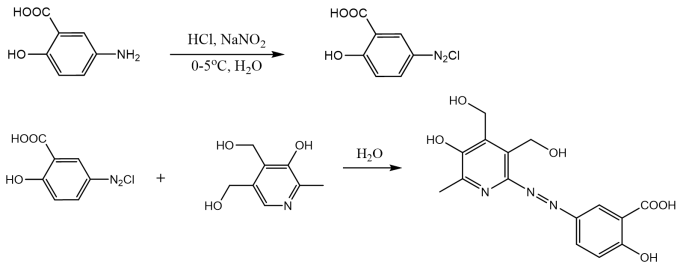

Figure 3. Compound Four Synthesis

and 10.39 ppm, respectively (Kleks et al., 2021). The H-N bond in the pyrrole ring and the CH=N bond in the azomethine group was responsible for two additional signals at δ 9.25 and 8.61 ppm, respectively (Jasim et al., 2020). The multiple signals observed at the 6.53-8.13 ppm range for six protons corresponded to the aromatic protons of pyrrole and salicylic rings.

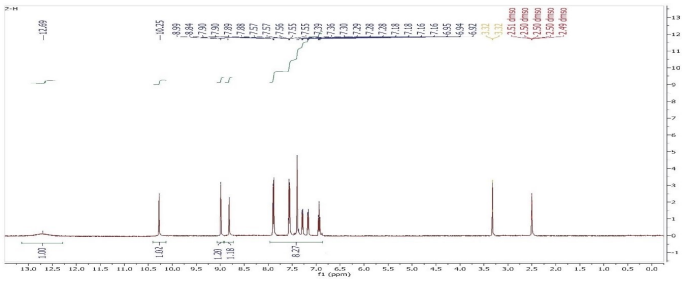

Figure 4. Spectrum of ^{1}H-NMR Compound 2

Singlet signals were observed in the ^{1}H-NMR spectrum of compound 2 at δ 12.69 and 10.25 ppm. These signals were ascribed to the salicylic acid fragment's phenolic hydroxyl and carboxylic hydroxyl protons. Another two singlet signals were observed at chemical shifts of δ 8.99 and 8.84 ppm, attributed to the N-H of indole and CH=N of the azomethine group, respectively. Figure 4 shows several aromatic signals between δ 6.92 and 7.90 ppm, caused by the eight indole and salicylic acid group protons.

Aromatic amines react with concentrated HCl and sodium nitrite at 0-5 °C to produce diazonium salts. Sulfamethoxazole or 5-aminosalicylic acid subjected to diazotization process to give the corresponding diazonium salts. Another step in the

synthesis of an azo compound is coupling reaction with rich electron aromatic system, diazonium salt of sulfamethoxazole reacts with 5-aminosalicylic acid to give the azo compound (3). Azo compound (4) was synthesized by reaction of diazonium salt of 5-aminosalicylic acid with pyridoxine with characteristic bright colored crystals, as shown in Figure 2 and 3.

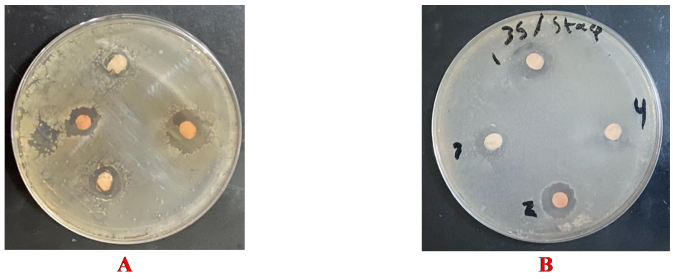

Figure 5. (A) IZ of Compound (1) Against *E. coli*, (B) IZ of Compound (4) Against *S. aureus*

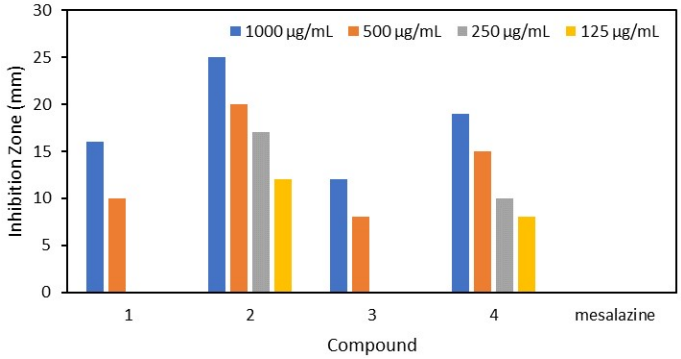

Figure 6. Inhibition Zone of the Studied Compounds Against *S. aureus*

The IR spectra of the azo compounds gave broad peaks at the range about v 3400 cm^{-1} due to stretching vibration of O-H of carboxylic group overlapped with phenolic group. Another characteristic strong-medium peak attributed to stretching vibration of azo group appeared at 1463 and 1587 cm^{-1} for compound (3) and (4), respectively.

^{1}H-NMR of the compound (3) gave two singlet signals in download field at δ 12.56 and 10.40 ppm attributed to hydroxyl group of carboxylic and phenolic groups, respectively. Another singlet signals at δ 11.20 ppm attributed to N-H proton of amide in sulfa fragment and at δ 5.36 ppm due to two protons of NH_2 group in salicylic fragment. Aromatic protons gave multiplet signals at the range δ 6.86-8.02 ppm referred to seven protons in each sulfa and salicylic fragments, and finally, singlet signal at highfield range δ 1.91 ppm attributed to three protons of methyl group, as shown in Table 1.

The ^{1}H-NMR analysis of compound 4 yielded a complex spectrum featuring two singlet signals at δ 12.77 and 10.35 ppm, which were attributed to the hydroxyl proton of the

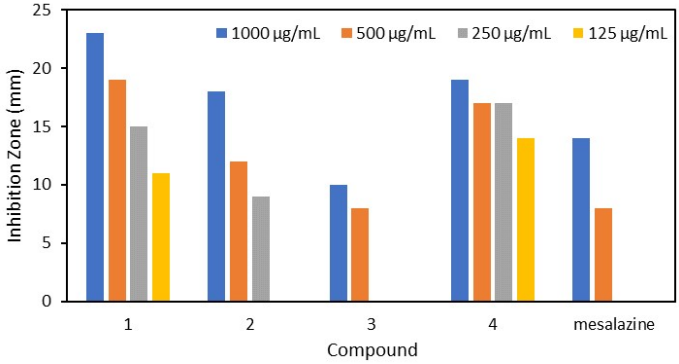

Figure 7. Inhibition Zone of the Studied Compounds Against *E. coli*

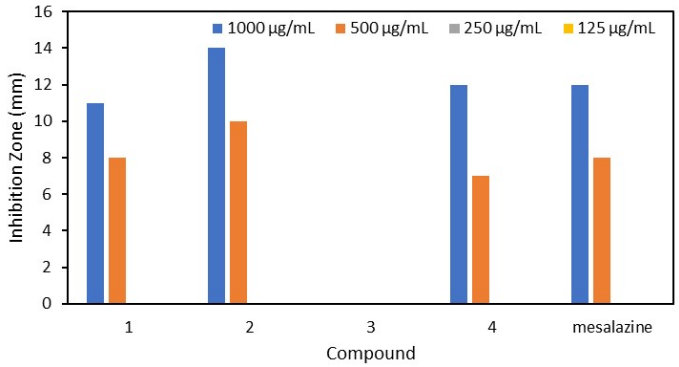

Figure 8. Inhibition Zone of the Studied Compounds Against *P. aeruginosa*

phenolic and carboxylic groups, respectively. A singlet signal at δ 9.79 ppm was also observed, which was attributed to a single phenolic proton of the pyridoxine group. Multiplet signals at δ 6.62-7.37 ppm referred to three protons of salicylic ring, singlet signal δ 5.63 ppm due to two protons of aliphatic alcohol, singlet signal referred to four aliphatic protons of two groups of methylene in -CH_2-OH fragment in pyridoxine ring at δ 4.21 ppm, Finally, as shown in Table 1, the singlet signal at δ 2.37 corresponds to the three protons of a methyl group in the pyridoxine ring.

3.2 Antibacterial Sensitivity Test

The activity of the synthesized compound was assessed through the disc diffusion method utilizing various concentrations (125, 250, 500, and 1000 μg/mL) while using DMSO as a control. The results were then compared to the standard drug mesalazine. Against *S. aureus* bacteria, compound (2) and (4) showed higher activity (25 and 19 mm, respectively) as compared other compounds. Against *E. coli* bacteria, the compounds (1, 2 and 4) gave strong inhibition zone (23, 18 and 19 mm, respectively) as compared with other compounds, as shown in Figure 5. The synthesized compounds exhibited considerable efficacy compared to the standard mesalazine drug, potentially due to the bacteria's resistance to the commercial

Table 1. ^{1}H-NMR Synthetic Compound's Data

Compounds	-COOH	-OH	-NH	-CH=N	δ (ppm) Aromatic	Others
1	12.80 (s)	10.39 (s)	9.25 (s)	8.61 (s)	6.53-8.13 (m)	-
2	12.69 (s)	10.25 (s)	8.99 (s)	8.84 (s)	6.92-7.90 (m)	-
3	12.56 (s)	10.40 (s)	11.20 (s)	-	6.86-8.02 (m)	5.36 (s) -NH_2, 1.91 (s) -CH_3 Pyridine ring, 9.79 (s) -OH, 5.63 (s)
4	12.77 (s)	10.35 (s)	-	-	7.25-7.86 (m)	aliph. -OH, 4.21 (s) -CH_2-, 2.37 (s) -CH_3

ppm: part per million, s: singlet signal, m: multiplet signal

Table 2. In Vitro Antibacterial Sensitivity Test of Synthesized Compounds in DMSO

Concentration (μg/mL)	*S. aureus*	*E. coli*	*P. aeruginosa*
	IZ (mm) Compound (1)		
1000	16	23	11
500	10	19	8
250	Nil	15	Nil
125	Nil	11	Nil
	IZ (mm) Compound (2)		
1000	25	18	14
500	20	12	10
250	17	9	Nil
125	12	Nil	Nil
	IZ (mm) Compound (3)		
1000	12	10	Nil
500	8	8	Nil
250	Nil	Nil	Nil
125	Nil	Nil	Nil
	IZ (mm) Compound (4)		
1000	19	19	12
500	15	17	7
250	10	17	Nil
125	8	14	Nil
	IZ (mm) Mesalazine		
1000	Nil	14	12
500	Nil	8	8
250	Nil	Nil	Nil
125	Nil	Nil	Nil

drug. Overall view on the activity, the best activity is 23 mm attributed to (1) against *E. coli* and 25 mm for compound (2) against to *S. aureus*, as shown in Figure 6-8. Table 2 represents the data of in vitro antibacterial activity of synthesized compounds in DMSO.

Schiff bases with a salicylic-imine moiety are also effective in the mechanism of inhibition on bacterial growth. Compounds 1 and 2 belonging to this category of Schiff bases exhibited complete growth inhibition against *S. aureus* and *E. coli* (Tyagi et al., 2017; Kumar and Bansal, 2021).

Regarding *P. aeruginosa*, the highest antibacterial activity was detected by compound 2 with a minimum zone of inhibition of about 14 mm which was the weakest inhibition zone among other studied bacteria, moreover, *P. aeruginosa* shows complete resistance to compound 3 whatever its concentration was.

4. CONCLUSION

The Schiff bases, denoted as compounds 1 and 2, and the azo compounds, designated as compounds 3 and 4, were successfully synthesized with high yield and purity. Subsequently, spectroscopic techniques were employed to characterize these compounds. The inhibition zone method evaluated the synthesized compounds' antibacterial sensitivity. Compounds 1, 2, and 4 demonstrated intense activity against *S. aureus* and *E. coli*, while compound 3 exhibited moderate activity. The bacteria *P. aeruginosa* showed high resistance against the synthesized compounds. The standard drug mesalazine showed weak activity under the same experimental conditions, which referred to the high resistance of all three strains of bacteria to this known drug. Another finding from this study is that the ability of synthesized compounds to inhibit bacterial growth increased with increased concentration.

5. ACKNOWLEDGMENT

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